Program/Abstract # 126
MiR-221 and miR-130 regulate Hox genes controlling vascular morphogenesis in developing lung
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Hoxa5 and Hoxb5 have distinct important functions in lung airway and alveolar formation. In other cell types, Hoxa5 and Hoxb5 have opposing roles in vasculogenesis and are regulated by miR-130a and miR-221, respectively. Hoxb5 and Hoxa5 regulation by these miRNAs in developing lung is unknown. We have previously reported unique changes in miR-130a and miR-221 temporal and cellular expressions in E15–18 fetal mouse lungs. Lung-specific effects of miR-130a and miR-221 were studied in mouse E14 whole lungs cultured 48 h with anti-miRs or mimics to miR-130a and miR-221. Anti-miR-130a treatment led to smaller lungs with reduced airway branching with increased Hoxa5 and decreased VEGFR2 in mesenchyme. Mimic 130a treated lungs had numerous finely arborized branches extending into central lung regions with decreased Hoxa5 and increased VEGFR2 in mesenchyme. The distal airways of these lungs were lined with cuboidal cells. Conversely, anti-miR-221 treated lungs had more distal branch generations with increased Hoxb5 and VEGFR2 around airways. Mimic 221 treated lungs had reduced airway branching, dilated airway tips and decreased Hoxb5 and VEGFR2 in mesenchyme. Vascular morphology (Lectin immunofluorescence) showed that miR-221 inhibition and miR-130 enhancement of vascular plexus formation likely impact lung airway branching. MiR-130a and miR-221 temporal, spatial and cell-specific expressions and their opposing effects on airway branching support lung-specific regulation of Hoxa5 and Hoxb5 expressions by miR-130a and miR-221, respectively. We speculate that miRNA–Hox regulatory interactions in developing lung contribute to vascular and epithelial differentiation.

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Program/Abstract # 127
Control of Lymphangiogenesis by Prox1
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In mammals, the proper function of the blood and lymphatic vascular networks is critical for effective circulation. Blood vessels deliver nutrients and oxygen, while lymphatic vessels are essential for lipid absorption, fluid homeostasis, and immune surveillance. In addition, lymphatic vessels are involved in a variety of pathological conditions such as obesity and tumor metastasis. Previous studies have shown that the prospero-related homeobox gene Prox1 is a master regulator of lymphatic lineage specification. During early embryonic development, expression of Prox1 on one side of the anterior cardinal vein is considered the initiation of lymphatic vascular formation. In mice, deletion of Prox1 results in the absence of the lymphatic vasculature and the mutants develop severe edema. In addition, ectopic expression of Prox1 in cultured blood endothelial cells (BECs) promotes the expression of lymphatic endothelial cell (LEC) markers and reduces that of BEC markers. To better understand the molecular mechanisms leading to LEC fate specification by Prox1, we generated transgenic mice that ectopically express Prox1 in a spatially and temporally controlled manner. We observed that ectopic expression of Prox1 in BECs in mice results in abnormal expression of the LEC maker LYVE-1 in the internal jugular vein. In addition, dermal blood vessels show irregular morphology. Furthermore, the formation of lymphatic vessels in these animals is significantly reduced, with lymphatic vessels that are dilated, hyperplastic and filled with blood.

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Program/Abstract # 128
The transcription factor FoxO1 is required in endothelial cells for vascular remodeling of the mouse yolk sac
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The initial vascular network of the mouse yolk sac, formed by embryonic day 8.0 (E8.0), is a primitive capillary plexus of vessels of uniform shape and size. At the initiation of blood flow (E8.5), this plexus undergoes vascular remodeling, in which endothelial cells establish a branched, hierarchical structure of large vessels and smaller capillary beds, evident by E9.5. Embryonic lethality due to failed remodeling is a common phenotype observed in over 80 single gene mutations, and may be due to a primary defect in endothelial cell function or reductions in hemodynamic function. However, in a large number of yolk sac mutants, the direct causes of the observed vascular remodeling defects are still unknown. FoxO1 germline null (−/−) mice have been reported to die by E11.0 due to abnormal vascular remodeling; however, the primary cause of the remodeling defect remains unclear. In this study, we conditionally delete FoxO1 in endothelial cells (ECs) and show that its function during embryonic development is critical for the formation of a remodeled yolk sac vasculature. Using live, rapid-time lapse imaging, we verify that the remodeling defects are not due to altered hemodynamic force. We observe that FoxO1 deletion in ECs in vivo leads to the downregulation of angiogenic genes, including connexins 37 and 40, which causes an increase in vascular permeability within the embryonic yolk sac. Finally, we observe a reduction in the density of ECs within the mouse yolk sac in both pre-remodeling and post-remodeling stages. These data suggest that FoxO1 expression in ECs is critical for the formation of a capillary plexus before the onset of hemodynamic force, resulting in impaired yolk sac remodeling and embryonic lethality.

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Program/Abstract # 129
Interactions between vascular cells and neuron-glial cells in the developing central nervous system under hypoxia in vitro
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The lack of information on the biology of the neurovascular unit explains the few therapeutic treatments available for neurodegenerative diseases and the increasing interest on the cell biology in this field. In this context, in vitro analyses of interactions between developing vascular and neuron–glial cells appear as a valuable method to investigate neuroangiogenesis. Recent in vitro studies on the developing vasculature in the chick embryo optic tectum (OT) allowed to immunochemically identify and quantify several vascular and neural cells types after 15 days in vitro culture under normoxia. More recently, the effect of acute hypoxia on the different cell types were studied in cells cultures containing a mixture of all these cell populations.